EXHIBIT A

Head Lice Information

HARVARD SCHOOL OF PUBLIC HEALTH

("Harvard Study")

Harvard School of Public Health

HEAD LICE INFORMATION
statement from Richard J. Pollack, PhD

Download:

information sheet (700 K)

information sheet, no graphics(44 K)

form to document infestation (19 K)

Head lice: Information and Frequently Asked Questions

Infestations by head lice become most apparent at the beginning of each school year. Parents, day care providers, school officials and healthcare professionals frequently seek information and solutions to this burdensome problem. Accordingly, we have provided answers to frequently asked questions concerning this subject. We hope this information will be useful.

What are head lice, and how do they differ from other lice? Head lice (*Pediculus capitis*) are small parasitic insects exquisitely adapted to living mainly on the scalp and neck hairs of their human host. Their six impressive legs are elegantly evolved to grasp hair shafts and provide a striking example of biological specialization. Long associated with people, head lice have been recovered from prehistoric mummies. Head lice are equal opportunity parasites; they do not respect socio-economic class distinctions. Their presence does not connote a lack of hygiene or sanitation practiced by their host. Head lice are mainly acquired by direct head-to-head contact with an infested person's hair, but may infrequently be transferred with shared combs, hats and other hair accessories. They may also remain on bedding or upholstered furniture for a brief period. In North America and Europe, children are more frequently infested than are adults, and Caucasians more frequently than other ethnic groups. Neither able to fly nor jump, lice are also unlikely to wander far from their preferred habitat. Lice and their eggs are unable to burrow into the scalp. Lice are sometimes referred to as *cooties*, eggs as *nits* and infested people as *lousy*. The infestation by head or body lice is termed *pediculiasis*, and the associated "disease" *pediculosis. Delousing* (more properly termed *lousing*) consists of any method for eliminating an infestation. Chemical treatments directed against lice are *pediculicides.* Those that kill adult and nymphal lice are sometimes called *lousicides;* those that kill the developing embryo within the egg are *ovicides*. This discussion relates to head lice unless specific mention is made of other types of lice.

Head lice derive nutrient by blood-feeding once or more often each day, and cannot survive for more than a day or so at room temperature without ready access to a person's blood. A nymphal louse hatches from its egg after about 8 days of development, and begins to feed, grow and develop until it attains the adult stage about 9-12 days after hatching. A female louse may deposit more than 100 eggs at a rate of about six eggs each day. Only those eggs deposited by inseminated female lice will hatch. Generally, an infested person has fewer than a dozen active lice on the scalp at any time, but may have hundreds of viable, dead and hatched eggs. With adequate magnification, the developing nymph can be seen within the egg; hatched eggs are nearly transparent (see photos accompanying this site).

Treatment should be considered only when active lice or viable

eggs are observed. Itching of the scalp or the perception that something is crawling on the head do not warrant treatment for lice. Without magnification and suitable experience, they may be difficult to correctly distinguish from other material caught in the hair. Amongst presumed "lice" and "nits" submitted by physicians, nurses, teachers and parents, most are simply artifacts such as dandruff, hairspray droplets, scabs, dirt, or other insects (e.g. aphids blown by the wind and caught in the hair). To confirm the identity of suspected material, save a few lice and louse eggs under clear tape on our specimen submission form, and record the requested information. Submit the samples to us or to a qualified physician or entomologist to confirm the identity of the offending creatures (to learn more about this, visit the section: **Specimen evaluation**).

Body lice (*Pediculus humanus*) are closely related to head lice, but are less frequently encountered in the US. As the name implies, body lice generally feed on the body, but may rarely be discovered on the scalp and facial hair. They usually remain on clothing near the skin, and generally deposit their eggs on or near the seams of garments. Body lice are acquired mainly through direct contact with an infested person or their clothing and bedding, and are most commonly found on individuals who infrequently change or wash their clothes. A change to clean clothes, and laundering of infested garments (especially drying with high heat or ironing), are generally effective to eliminate this burden.

Body lice (but not head lice or pubic lice) serve as vectors of certain human pathogens. Epidemics of louse-borne typhus, louse-borne relapsing fever and trench fever decimated the populace through the ages, and millions more perished from these infections during the 1900's during major conflicts and famines. Fear of these diseases fueled atrocious and perverse campaigns to quarantine and assault unpopular ethnic groups suspected of promoting risk. Current efforts to seek out and quarantine individuals infested with head lice may be driven, in part, by those who misinterpret or intentionally misapply certain principals of public health.

Pubic or crab lice (*Pthirus pubis*) have a short crab-like body easily distinguished from that of head and body lice. Pubic lice are most frequently found around the pubic region of the infested person, but may also be found elsewhere on the body (including facial hair and eyelashes). The infestation by pubic lice is termed *pthiriasis*. Mechanical removal of these lice and their eggs is the preferred method of treatment. Because pubic lice are acquired mainly through sexual contact, their presence may be associated with other sexually-transmitted diseases. Pubic lice on a child may cause the physician to consider the possibility that the child may have had inappropriate contact. Pubic lice may also be acquired through more innocent means, such as by sharing a bed with an infested person.

Book, bark, beggar's and sea 'lice' are quite unrelated to human biting lice. Book and bark lice are insects commonly found in organic material such as leaf litter, under bark of trees, and even within the pages of books. Book lice, when abundant, can cause damage to books and are considered pests in library collections. Book and bark lice are occasionally submitted for identification as presumed parasites. Their presence on a person's body is merely incidental; they do not parasitize people. Diverse types of plant seeds adhere to clothing and hair, and are commonly termed "beggar's lice." Some insects related to aphids are known as "plant lice." Certain parasites of fish are known as 'sea lice", but this term is often misapplied to a condition known as 'seabathers' eruption" that seasonally affects bathers along the seacoasts (apparently due to contact with stinging cells of certain jellyfish). Finally, although diverse types of lice parasitize mammals and birds, these rarely affect people.

Cryptic infestations Some people earnestly believe that they are actively infested, even though no louse or other parasite can be detected. These cases can be particularly difficult to manage, and the affected individual should not be dismissed as being unstable. Every reasonable effort should be explored to identify the cause of the irritation and to capture and identify any offending creature on the scalp or body. The irritant may, indeed, be a louse or some other type of biting insect or mite, but may not necessarily be infesting the person at the time of examination. Diverse insects (e.g. mosquitoes, fleas, bedbugs) may only transiently visit a person, and may or may not be noticed in the act of biting. Certain mites associated with bird nests occasionally wander into a house and cause annoyance. Itching and irritation in some cases may also be ascribed to hair care and laundry products, industrial fibers, underlying disease, or even to the pediculicidal (anti-louse) treatment. The clinician will often find it valuable to consult with an entomologist on these matters (to learn more about this, visit the section: Specimen evaluation).

A few people remain convinced that their infestation is real, even though they have been examined by one or more competent specialists who can find no physical cause for their discomfort. Some of these patients may pose a danger to themselves and others by resorting to the use of toxic or flammable substances in attempts to rid themselves of their real or perceived infestation. Such a person may, indeed, be delusional, and should be treated with care and respect when referred for counseling. Certain people develop an extreme phobia or irrational fear that they will acquire lice or other parasites from virtually any animate or inanimate object. Patients that are unduly burdened by this condition are likely to benefit from counseling with a clinician specializing in phobias and obsessive-compulsive disorders.

Do head lice cause harm? Head lice rarely (if ever) cause

direct harm, and they are not known to transmit infectious agents from person-to-person. Thus, they should not be considered as a medical or a public health problem. These lice may occasionally be burdensome because of annoyance; their presence may cause itching and loss of sleep. The louse's saliva and feces may sensitize people to their bites, thereby exacerbating the irritation and increasing the chance of secondary infection from excessive scratching.

The greatest harm associated with head lice results from the well-intentioned but misguided use of caustic or toxic substances to eliminate the lice. A few lice on the head should not cause alarm; rather, they present an opportunity for parents to spend the needed time with their children in order to find and remove the offending insects. Grooming can be an effective method to remove lice, and engenders several associated physiological and behavioral benefits as well. Because of unfounded fears, some parents have suggested that children refrain from sharing protective batting or biking helmets. The miniscule risk of acquiring lice from such devices pales in comparison to the hazards averted by helmets.

Why were my children sent home from school (the No Nits policies)? The *no-nits* policies variously drafted and adopted by school administrations aim to reduce the transmission of lice by excluding infested children from school. Whereas these policies are meritorious in principle, they are virtually always counterproductive when applied. School nurses are generally amongst the most capable to spot signs of infestation, but lack the expertise and equipment to distinguish active from inactive infestations. School personnel and parent volunteers often conduct mass-screenings in misguided and failed attempts to identify infested children and ensure their treatment. Concerned parents, nurses and school administrators may find it valuable to cooperate by drafting rational policies. *The discovery of lice or their eggs on the hair should not cause the child to be sent home or isolated. Furthermore, treatment is not indicated if the infestation is not active.*

Although lice and their eggs may be seen without the help of magnifying devices, the viability of the eggs cannot be judged without magnification and a degree of training. Of more than six hundred samples of presumed lice and nits submitted to us for examination, fewer than two-thirds contained evidence of any infestation. The remainder of the samples were composed of miscellaneous insects or of artifacts that resembled eggs. Of those samples that did contain bona-fide louse eggs, many were comprised solely of hatched or dead eggs; thus, no treatment would be warranted. We noted that:

1. health care professionals as well as non-specialists frequently over-diagnose this infestation,

2. non-infested children are quarantined as often as infested children,
3. traditional pediculicides and alternative formulations are frequently over-applied

Because pediculiasis is generally misdiagnosed, and because few symptoms and no direct infectious processes are know to result from an infestation, we suggest that the practice of excluding presumably infested children from school is unwarranted.

The full citation of our published article is:

Pollack RJ, Kiszewski A, Spielman A. Overdiagnosis and consequent mismanagement of head louse infestations in North America. Pediatric Infectious Disease Journal. 2000; 19:689-693.

The abstract and article may be accessed through the Journals web site: http://www.pidj.com/

Although head lice are transmissible, their potential for epidemic spread is minimal. Indeed, the basic reproduction number (a measure that defines the number of secondary infections arising from an index case) would be far lower for head lice than for infections due to cold or flu viruses - yet children are rarely excluded from school because of these often more-debilitating infections. Furthermore, we are unaware of any convincing data that demonstrates that enforced exclusion policies are effective in reducing the transmission of lice. These quarantine policies seem a disagreeable vestige of certain offensive and supposedly health-based anti-ethnic strategies practiced mainly in Europe earlier this century. It is our professional opinion that the *no-nits* policies are imprudent, as they are based on intolerance, hysteria and misinformation rather than on objective science.

Lice on children's heads, by themselves, should not be cause for the schools or courts to brand the parents as 'neglectful' or 'abusive'. We are aware of several cases where the courts have ordered children removed from the custody of their parents because of their apparent failure to eliminate the infestations. Such extreme actions to an infestation are generally unwarranted and may suggest poor judgment on the part of those making policy decisions. We are also aware of legal actions brought against the schools by the parents of children who have been excluded from school. These actions should now prompt school administrators to reevaluate their practices of identifying infestations as well as their exclusion policies and treatment recommendations. *We encourage parents and school administrators affected by these policies to send us details of their cases.*

From whom did my child acquire head lice? Head lice are acquired from other infested people. Upon learning of their child's

infestation, parents frequently seek to ascribe blame. This 'knee-jerk' reaction is understandable but unproductive. The offending lice came from some other person, but it is not currently possible to determine the identity of the donor. Parents are encouraged to focus their energies on education and treatment rather than on unsuccessful witch-hunts. Rather than accusing the school administrators or other parents for not preventing spread of head lice, parents are likely to benefit more by ensuring all children and adults in the home are inspected and treated as appropriate.

What is the origin of head lice? Human lice likely co-evolved with people. Our primate relatives harbor their own species of lice. Lice are quite host specific; human lice, for instance, will not feed upon other animals, and lice of other animals would rarely feed upon a person.

How many people are infested by head lice? Few useful statistics are available for estimating the prevalence of infestation. Far fewer people seemed infested than the general public or the medical community might believe. Reports of "epidemics" of head lice may generally be attributed to incorrect identifications and misdiagnoses. The apparent annual and seasonal "increases" in prevalence may be real or due to peculiarities in monitoring activities. The perception that lice are more prevalent today then in past decades may, perhaps, reflect societal changes in candor in discussing such issues

What methods can I use to treat the infestation? First, ensure that a correct diagnosis/identification has been made before considering treatment options. An old infestation, manifested solely by hatched eggs, is not a cause for treatment. Treatment should be considered only when active lice or viable eggs are observed (refer to the images of lice and eggs). Several options exist to eliminate the infestation, but some are better tested than others. Success will likely depend on an integrated approach that relies on several of the methods listed below, combined with perseverance and a bit of levity. Because the egg is particularly resistant to some chemical treatments, a second treatment is often required about 10 days later to target the nymphs that hatch after the initial treatment. We have drafted **management schemes** to assist the parent and school administrator.

a) Misdiagnosis (no active infestation, or misidentification),

b) Non-compliance (not following treatment protocol)

c) Resistance by lice to the insecticide

d) New infestation (lice acquired after treatment)

e) Lack of ovicidal (egg-killing) or residual properties of the product.

Reports of resistance or lack of sensitivity to insecticides by head lice in other countries have been published in the scientific literature, and non-peer-reviewed reports abound elsewhere. Accordingly, we investigated whether head lice in the US had developed resistance or tolerance to pyrethroid insecticides. We developed a bioassay to test the responses of lice to permethrin, and identified infested children who could provide us with the needed samples. Our findings were published in a peer-reviewed medical journal. In brief, we reported that:

1) head louse infestations in the US are surprisingly infrequent,

2) head lice sampled from children who were chronically-infested and treated multiple times with pyrethroid shampoos tend to be resistant to permethrin,

3) head lice sampled from children living where pyrethroids are rarely used against lice (Malaysian Borneo) tend to be susceptible to permethrin,

4) lice that are resistant to permethrin at low doses are generally resistant to high doses as well; thus prescription formulations of containing permethrin at concentrations of 3-5% are unwarranted,

5) the prevalence of resistance to permethrin has yet to be determined. This final point is of critical importance in understanding the significance of our findings. In our report we document the existence of permethrin-resistant head lice in the United States. This should not be interpreted as meaning that all (or even most) head lice are resistant to permethrin and related compounds. Permethrin and pyrethrins remain the treatment of choice for newly-identified infestations. If live lice persist following such treatments, then one may consider that these lice may be resistant to this family of insecticides. Further treatment may be warranted with pediculicides containing other insecticides. Refer to the discussions on malathion and lindane elsewhere on this web site.

The full citation of our published article is:

Pollack RJ, Kiszewski A, Armstrong P, Hahn C, Wolfe N, Rahman HA, Laserson K, Telford SR III, Spielman A. Differential Permethrin Susceptibility of Head Lice Sampled in the United States and Borneo. *Archives of Pediatrics and Adolescent Medicine.* 1999;153:969-973

The full article can be viewed on the American Medical Association's web site: http://archpedi.ama-assn.org/issues/v153n9/toc.html

Do insecticides cause resistance? Insecticides generally do not cause mutations leading to insecticidal resistance. Rather, any insect (or any organism) may, by chance, have the capacity to avoid, detoxify or eliminate toxins from its body. These few individuals may survive treatment, reproduce and serve to establish a larger population of lice that are less susceptible to that insecticide and perhaps to related compounds.

Mechanical removal Mechanically removing lice and nits can be an effective but time-consuming method. Because most eggs will be non-viable, their removal is often impractical and unjustified. An infestation may be eliminated by combing each day to remove the live lice (including those that have hatched since the previous day). Comb daily until no live lice are discovered for about two weeks. Use illumination, magnification and a good louse or nit comb to locate and remove the offending insects. Although the hair may appear 'peppered' with eggs, there generally are fewer than a dozen active lice on the head at any time. Adult female lice usually cement each egg to the base of a hair shaft near the skin. As the hair grows (from the base), these attached eggs are transported away from the scalp. Eggs more than one-half of one inch away from the scalp are nearly always hatched and do not, by themselves, indicate an active infestation.

Louse or nit combs can be useful in removing lice and eggs. Diverse types of fine-toothed combs may be included within packages of pediculicides or they may be purchased from virtually any drug store, pet supply store (often at a discount) or via the web. Some louse combs are better than others; their effectiveness depends on a) their composition (metal vs. plastic) and construction (length and spacing of the comb teeth), b) the texture of the hair to be combed, c) the technique used to comb, and d) the time and care expended in the effort. Whereas straight hair is usually readily combed, tight curls may present an impossible and impractical challenge. Hair should be cleaned and well-combed or brushed to remove tangles before attempting to use a louse comb. Clean the louse comb frequently to remove any caught lice or eggs. It may require several hours each night for several nights to tackle the problem. An entertaining video may help keep the child occupied during this exercise. Sit behind the child, and use a suitably bright light (and magnification if available), to inspect and comb through the hair, one small section at a time. Repeat until no more active lice are observed. Some parents report that water, vegetable oils or hair conditioners help lubricate the hair and ease the combing process; others report that these lubricants make it more difficult to see the eggs.

"Electronic" louse combs that resemble small bug "zappers", or those with oscillating teeth would seem to offer little advantage, if any, over a well-designed traditional louse comb. Teeth of these devices may not effectively reach to the scalp and may not kill or remove eggs.

Pyrethroid insecticides Infestations may be treated with shampoos containing permethrin or pyrethrins specifically labeled for use on people. Some formulations also contain a synergist, a chemical that may enhance the activity of the insecticide. As with any insecticide or drug, read and follow the label directions. Because these products seem to have limited ovicidal (egg-killing) activity, a second treatment is often necessary about 10 days later to target lice that hatch after the initial treatment. Susceptible lice do not fall from the hair or die immediately upon treatment with pyrethroids; one should wait until the next morning to determine the fate of treated lice. As is true of any pediculicide, pyrethroids do not remove the eggs from the hair.

Some physicians treat apparently resistant infestations with a prescription-strength pyrethroid (3 - 5%) preparation normally meant for treating scabies infestations. In our recently published article we report that some head lice in the United States are resistant to permethrin, and that higher doses of this insecticide generally were not more effective. Thus, prescription-strength pyrethroids are not likely to be effective. Although permethrin and pyrethrins differ in chemical structure, their mode of action is quite similar. Thus, we would anticipate that pyrethrins would also be ineffective in killing permethrin-resistant lice.

Non-pyrethroid insecticides Other insecticides should be avoided unless specifically prescribed by a physician. The organochlorine insecticide lindane, and the organophosphate insecticide malathion are two of the active agents within pediculicides available by prescription. The current susceptibility of these insects to lindane or malathion has not yet been analyzed in the United States. Prescription preparations containing these insecticides may be considered as alternative pediculicides if live lice persist after two treatments with pyrethroid-based pediculicides. Refer to our management flowcharts.

Use caution when dealing with any insecticidal agent, particularly on children. Read and follow label directions. Do not apply any insecticide or other chemical not specifically labeled for use on people. Well-intentioned parents treating their children with toxic or flammable substances have caused several deaths and poisonings.

Essential oils Numerous "home recipes" and commercial preparations are based on mixtures of essential oils, salts or other "natural" substances. Data is lacking to support the claims of their

efficacy. Several formulations include substances that should not be used on the skin, and may not be registered for such use by government regulatory agencies (such as EPA or FDA).

Enzyme treatments The chemical structure of the "cement" that binds the egg to the hair is not well-defined. Nonetheless, it is an exceptionally stable substance that resists degradation by diverse chemicals. Several commercial products are advertised to "dissolve" the eggs or the cement by which the eggs are attached to the hair. We are not convinced of the effectiveness or safety of these products.

Antibiotics The guts of human lice contain a specialized organ that harbors an unusual type of bacteria. These bacteria may aid the louse in digesting the blood meal or by providing essential nutrients. Certain antibiotics may affect or eliminate these bacteria from the louse's gut, and body lice that have fed upon antibiotic-laden blood of people may be burdened and die. The effect of antibiotics on the health of head lice has yet to be determined conclusively. Physicians increasingly seem to prescribe combinations of the antibiotic agents trimethoprim and sulfamethoxazole (e.g. "Bactrim", 'septra") in attempts to treat head lice. We oppose this practice because these antibiotics are not approved as pediculicides, and they are valuable in fighting life-threatening infections. Their use for treating such a relatively innocuous condition as a louse infestation may accelerate the emergence or spread of bacterial resistance, thereby diminishing the usefulness of these antibiotics.

Antiparasitic drugs Diverse antiparasitic agents have been proposed for treating human lice, but none has been evaluated critically. The drug ivermectin, for example, is widely used in veterinary medicine as an antiparasitic agent, and is available for human use for treating infestations caused by certain worms; it is not approved for use against human lice. Accordingly, we suggest that such treatments be avoided.

Suffocating agents An increasingly popular "alternative" treatment involves the use of food-grade oils or hair gels in attempts to smother lice on the scalp. Many people have provided anecdotal reports of their successes with this old method, but we have also heard of nearly an equal number of failures. Virtually no data, however, is available to assess the efficacy of this technique. As with any hair conditioner, oils may lubricate and ease efforts to pass louse or nit combs through the hair. Olive oil (or any similar food-grade product) would seem intrinsically safe, but may have associated hazards, nonetheless. Oil may cause accidents (slips), and would be difficult to remove from the hair and scalp (detergents can cause irritation). Do not use motor or machine oils, as these materials can be harmful.

As a preliminary test to measure the effect of such agents on lice, we submerged six active lice in olive oil, and maintained an equal number of non-treated lice in a separate container. Lice removed from oil after one hour recovered, but those submerged for two hours succumbed. Non-treated lice survived for at least 18 hours. We have not repeated this test on active lice nor have we tested this treatment on nits. The results are simply of a very preliminary nature and should not be construed as solid evidence on which one would base treatment recommendations. It would be an error to extrapolate from data of such an informal test; therefore, we do not recommend the use of olive oil (or other such substances) as a treatment for head lice.

Heat The hot dry air produced by standard hand-held hair dryers may suffice to kill lice and their eggs on a person's hair. Use great care if you try this method, as the heated air from these devices can also easily scald the hair and the scalp. No precise values (treatment time, temperature, and distance from hair dryer) are available with which to base an objective treatment protocol. Heated curling irons, hair straighteners or similar devices may kill some lice and eggs, but may not safely be applied to hair nearest the skin where viable eggs are most abundant. A clothes dryer set a high heat or a hot pressing iron may effectively kill any lice or their eggs on pillowcases, sheets, nightclothes, towels and similar items that will not be damaged by this process. Combs, brushes, hats and other hair accessories in contact with an infested person should be washed in hot water each day to dislodge any lice or nits.

Freezing Lice and their eggs on inanimate objects (e.g. toys) may be killed by freezing temperatures. Objects that cannot be heated in a clothes dryer may be placed in a freezer (or outdoors if sufficiently cold). This treatment may require several days to be effective, depending on the temperature and humidity. Such treatment would rarely (if ever) be required.

Haircuts Lice will find little to grasp on a bald or shaved head. Although competitive swimmers who shave their heads generally need not be concerned about head lice, many parents may find this old-fashioned method to be aesthetically unappealing. Short hair is more readily searched for lice and eggs, but does not make the child invulnerable to infestation.

All three types of human lice may occasionally be found on the eyelashes or other facial hair. These lice should be mechanically removed with great care so as not to injure the eye; insecticides should be kept well clear of the eyes as well. Cosmetology practices and regulations often dictate that infested individuals be sent away by the barber or beautician, and any implements that contacted that person be properly cleansed.

Hair soaps, bleaches and dyes Washing the hair each day

may dislodge a few active lice; the remaining lice and eggs will be unaffected (but clean). Although hair bleaches and dyes are meant for use on the scalp, they can be caustic. Data is lacking to assess the efficacy of these products against lice. Thus, use of these products in attempts to "treat" lice should probably not be considered. Assertions that dandruff shampoos are effective in removing lice are probably due to misidentification of dandruff as lice.

Do dogs and cats serve to maintain or transfer head lice? Pets are of no significance in maintaining or transmitting human lice, and should not be treated for head lice.

Should I clean my house or car? Head lice and their eggs soon perish if separated from their human host. Removed lice survive just a day or so, and the eggs generally lose viability within a week. The chances of a live head louse or egg becoming reunited with a person would seem remote exceptionally. Accordingly, Herculean steps to clean lice from the house or car by intensive washing or vacuuming will result in a cleaner space, but are unlikely to significantly facilitate the goal of eliminating the lice from those residing in the home. A child's car seat cover may benefit from vacuuming, as a few errant lice or eggs may temporarily lodge there and survive for a day or so.

What should be cleaned? Washing and drying (with heat) the pillowcases, sheets, nightclothes, towels and stuffed animals may possibly eliminate lice and eggs that might otherwise reinfest a family member. Combs, brushes, hats and other hair accessories in contact with an infested person should be washed in hot water each day to dislodge any lice and nits. Shared helmets and headphones in schools or recreational settings may rarely and transiently harbor an occasional louse or nit; the effort necessary to effectively inspect and clean these devices, however, is not likely warranted. Shared lockers or coat hooks probably pose even less risk as sources of contamination. Any lice or nits that might detach in a swimming pool would likely be removed by the pool filter or should otherwise perish before they have a chance to contact a person. Closing a swimming pool because of lice is a hysterical overreaction.

Should I use insecticides in the house to rid it of lice? Insecticidal treatments targeted at lice within the school or home, in vehicles, or to carpets and furniture are generally unwarranted, and unnecessarily expose occupants to insecticidal residues.

Can anything be used to repel lice? The application of any substance to the hair with an expectation of repelling lice is unwarranted and may neither be safe nor effective. Head lice do not seem to be readily acquired naturally, and they may pose less risk than any "repellent" product.

How can I have specimens evaluated? Health care professionals and others may send us samples to confirm the identity of suspected lice and eggs. Patients are encouraged to first approach their doctor or nurse for assistance and to discuss treatment. Although we endeavor to reply to inquires, the volume of such requests may limit our ability to answer all requests. Submitted samples are considered for entomological identification, and are not considered as clinical laboratory specimens. A form is available for submitting samples for evaluation. Go to the Specimen evaluation form.

Management Schemes We have created two flowcharts to assist the parent and school administrator in managing head lice infestations.

These plans may be viewed at:

Scheme for managing presumed headlice infestations
Scheme for managing presumed headlice infestations in school

This document has been assembled to assist health workers and patients access information relevant to the diagnosis and treatment of head louse infestations. Brand names have not been mentioned, nor do we endorse any particular commercial product. This web site is intended for informational purposes and is not meant to substitute for the advice provided by a medical professional. Always consult a physician if you have personal health concerns.

Costs associated with assembling this information and responding to inquires are borne by our general laboratory funds. Please feel free to contact us if you found this information useful and are inclined to assist with support of our work. We encourage inquiries regarding the support of further research.

This page is maintained by:
Richard J. Pollack, Ph.D. rpollack@hsph.harvard.edu
Anthony Kiszewski, D.Sc. akisz@hsph.harvard.edu
Andrew Spielman, Sc.D. (see feature in HSPH web digest)
Department of Immunology and Infectious Diseases (DIID)
Laboratory of Public Health Entomology
Harvard School of Public Health
665 Huntington Avenue
Boston, Massachusetts 02115-6021 USA

EXHIBIT B

PEARLMAN AMENDMENT OF MARCH 5, 2001

PEARLMAN-2

#5/6
3/7/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Dale L. PEARLMAN
Application No.	:	09/491,114 Confirm. No. : 8111
Filed	:	January 25, 2000
For	:	METHODS AND KITS FOR REMOVING, TREATING, OR PREVENTING LICE WITH DRIABLE PEDICULOSTATIC AGENTS
Group Art Unit	:	1614
Examiner	:	Brian Kwon

FAX RECEIVED
MAR 05 2001
GROUP 1600

Palo Alto, CA 94301
March 2, 2001
by Facsimile

Hon. Commissioner for Patents
Washington, D.C. 20231

REPLY UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office action mailed January 18, 2001 (paper no. 4), applicant respectfully submits the following response.

IN THE CLAIMS:

Please cancel claims 29, 30, 31, and 38 without prejudice.

Please rewrite claims 5 and 25 to read as follows:

A1

5 (amended). The method of Claim 2 in which the dried agent remains on the body for a time sufficient to kill at least some of the lice prior to removal.

A2

25 (amended). The method Claim 2 in which the driable pediculostatic agent comprises water, cetyl alcohol, propylene glycol, sodium lauryl sulfate, stearyl alcohol, methyl paraben, propylparaben, and butylparaben.

IN PALM:

Please change the applicant's name from "Dale L. Bearlman" to --Dale L. Pearlman --.[1]

Interview Summary Record

The applicant and undersigned attorney of record thank the Examiner for extending the courtesy of a telephonic interview on February 28, 2001. During the interview, Dr. Pearlman discussed the invention, emphasizing: (1) the inventive method's obligate drying step, and (2) the test, set forth in the specification, for determining which compositions are operative in the method of the present invention. The undersigned attorney of record then discussed the Examiner's rejections under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 103.

[1] The error would appear to derive from the quality of the facsimile signature page of applicant's original Declaration under 37 C.F.R. § 1.63.

The Invention

Existing methods of treating lice have significant, and well known, disadvantages. For the most part, the disadvantages stem from the requirement that the remedies contain an active ingredient toxic to lice, only a handful of which have been approved for topical use on human subjects.

For example, repeated exposures over the years to this small number of toxic actives has selected for increasing resistance, and decreasing efficacy of existing remedies, in louse populations worldwide. Furthermore, the population at greatest risk of infestation is that which is itself at greatest risk, or is perceived to be at greatest risk, from the toxic actives in these remedies, namely children; parents are increasingly concerned about applying toxic ingredients, now needed in ever increasing concentration, to their children's hair and scalp. The need for toxic agents also precludes use of these compositions for prophylaxis in the at-risk population, leading schools to enforce complete quarantine from school of affected students until cure is demonstrated.

The present invention relates to new methods of treating ectoparasites, notably head lice, that have significant advantages over existing remedies.

The mechanism of action common to the methods of the present invention can be simply stated. A liquid composition applied to the affected area of the subject triggers the immersion reflex in the lice. The composition, dried *in situ*, maintains the lice in the immersion reflex until they suffocate. Without first triggering the immersion reflex, the method is ineffective, as the lice avoid the source of heat; without maintaining the immersion

reflex after drying, the method is ineffective, as the lice recover. Thus, the method is practiced with a class of compositions that can induce the immersion reflex in the liquid state and that can maintain the lice in the immersion reflex once dried.

Because the immersion reflex can be triggered without the use of toxic actives, the methods of the present invention can be practiced with nontoxic compositions. Elimination of toxic actives reduces, and perhaps eliminates, the risk of engendering resistance. Elimination of toxic actives eliminates the risk, and perceived risk, of aggressively treating children. Elimination of toxic actives permits prophylaxis of at-risk individuals, eliminating the requirement for quarantine. The methods are easy to administer to children, well tolerated, and highly effective.

Claim 1 as filed and as examined recites the basic therapeutic method:

> 1. A method of removing ectoparasites from a subject, said ectoparasites having an immersion reflex, comprising:
> a) applying to an area of the body having the ectoparasites an effective amount of a driable pediculostatic agent for a time sufficient to trigger the immersion reflex in said ectoparasites;
> b) drying said agent; and
> c) removing said ectoparasites and optionally said agent.

Three things must be emphasized about the compositions applied in step(a) of claim 1.

First, the compositions can be old in the cosmetic arts; indeed, a composition described as preferred in the specification and claimed with specificity in claim 25 as

filed, Cetaphil® Cleanser, is available commercially. Novelty and nonobviousness are conferred not by the chemical composition of the agent applied to the subject's hair, but by the affirmative step of thereafter drying the liquid composition *in situ* on the subject's body (step (b)).

Second, although many of the advantages of the present invention derive from the new-found ability to eliminate toxic actives ("pediculicides") from the treatment composition, the method does not exclude use of pediculicides in compositions that would otherwise be effective in the claimed method.

Third, the method of claim 1 cannot be practiced effectively with every known or conceivable liquid composition that can be dried at tolerable temperature. Indeed, the specification teaches explicitly that water cannot be used in the practice of the claimed method:[2] although water can effectively induce the immersion reflex in lice when applied to the hair,[3] if the water is evaporated before louse suffocation (as long as 8 hours after immersion), the louse recovers-- this is the reason that bathing and showering are insufficient to cure infestation.

Thus, claim 1 calls for application not of any and all driable liquid agents, but rather for application of a "driable pediculostatic agent."

> A pediculostatic agent is one that elicits the "immersion reflex" in lice, whereby the lice become immobilized as a consequence of

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[2] Specification p. 23, line 33 - p. 24, line 2.

[3] Exposure of the host to water is indeed believed to be the evolutionary motivation for development of an immersion reflex by these obligate aerobes.

> reflexes that have evolved to avoid suffocation. The lice remain immobilized while in contact with the driable pediculostatic agent in its wet form, and do not recover from the immersion reflex once the agent has been dried onto the lice.

Specification p. 6, lines 3 - 10.[4]

Because the definition of "driable pediculostatic agent" is functional, rather than purely structural, the specification provides a simple, reliable, test that can routinely be performed without undue experimentation to determine whether an agent functions as a driable pediculostatic agent suitable for use in the practice of the claimed methods (see p. 20, line 30 - p. 22, line 6). The specification further provides extensive guidance — notably from p. 22, line 13 - p. 31, line 30 — on the chemical compositions that are most usefully subject to such test, as well as three specific examples of driable pediculostatic agents useful in the practice of the present invention.[5] Experimental examples 2, 3 and 4 (specification pages 38 - 46) show the remarkable efficacy of these novel methods using one of the three identified species of driable pediculostatic compositions.

Amendments

Claims 1 - 39 as filed were examined and rejected. Claims 29 - 31, and 38 have been cancelled. Claim 5 has

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[4] See also p. 1, lines 15 - 16; p. 9, lines 31 - 32; p. 10, lines 15 - 24; p. 20, lines 30 - 34; p. 22, lines 21 - 25; p. 23, line 31 - p. 24, line 2; page 30, lines 21 - 23.

[5] BABY MAGIC® baby shampoo, SUAVE® Baby Care bath soap tear free formula, and CETAPHIL® Cleanser. (Specification p. 31, lines 3 - 11 and lines 23 - 25).

been amended to correct a clerical error identified by the Examiner. Claim 25 has been amended to replace the trademark "Cetaphil® Cleanser" with the chemical composition thereof; support for the amendment to claim 25 can be found at p. 31, lines 23 - 30.

Claims 1 - 28, 32 - 37, and 39 are thus presented for examination.

Claim objections

Objection under 37 C.F.R. § 1.75 has been obviated by cancellation of claim 38.

Rejections under 35 U.S.C. § 112, ¶ 1

The Examiner has rejected claims 1 - 39 under 35 U.S.C. § 112, first paragraph, on the ground that the specification does not enable practice of the claimed methods across the entire genus of driable pediculostatic agents. Applicant respectfully, but firmly, traverses this rejection.

The Examiner is charged with the initial burden of presenting a *prima facie* case of nonenablement. If "a specification disclosure . . . contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented,"[6] the Examiner must provide "reason[s] to doubt the objective truth of the statements contained [in applicant's

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[6] "How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971).

specification that are] . . . relied on for enabling support."[7]

Applicant's specification contains teachings commensurate in scope with applicant's claims. The teachings include a broad functional definition of pediculostatic agents,[8] a test for determining which agents meet the functional definition,[9] extensive guidance on the chemical compositions that are most usefully subject to such test,[10] three specific examples of driable pediculostatic agents useful in the practice of the present invention,[11] and experimental examples demonstrating efficacious use of one of the three identified species.

The Examiner has not, however, provided adequate "reason[s] to doubt the objective truth of the[se] statements," since the reasons advanced by the Examiner in his the Office action are based upon a mistaken reading of applicant's specification.

Although the Examiner suggests that "Applicants have stated on page 21 of the specification, [that] 'any individual agent is a pediculostatic agent'", the full context of the cited phrase clearly states otherwise:

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[7] *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971).

[8] "Driable pediculostatic agents" are broadly defined at specification p. 6, lines 3 - 10; see also p. 1, lines 15 - 16; p. 9, lines 31 - 32; p. 10, lines 15 - 24; p. 20, lines 30 - 34; p. 22, lines 21 - 25; p. 23, line 31 - p. 24, line 2; page 30, lines 21 - 23.

[9] Specification p. 20, line 30 - p. 22, line 6.

[10] Specification p. 22, line 13 - p. 31, line 30.

[11] BABY MAGIC® baby shampoo, SUAVE® Baby Care bath soap tear free formula, and CETAPHIL® Cleanser, specification p. 31, lines 3 - 11 and lines 23 - 25.

> Driable pediculostatic agents useful in the methods and kits of the present invention are characterized by their ability to induce an immersion reflex in lice in their wet form and to keep the lice in the immersion reflex once dried. *The following in vitro test can be conveniently used to determine whether* any individual agent is a pediculostatic agent, and can further be used for routine screening of agents . . . to identify those that can be used in the methods, compositions, and kits of the present invention. . . . (emphasis added)

Specification p. 20, line 30 - p. 21, line 7. Thereafter follows description of an *in vitro* test that can readily, and routinely, be performed by those of skill in the dermatologic arts to determine which agents meet the definition of "driable pediculostatic agent" and that can, therefore, be used effectively in the claimed methods.

Absent reason to doubt the statements in applicant's disclosure, the "specification disclosure . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112. . . . "[12]

That said, it is indeed true that the phrase "driable pediculostatic agent" comprehends a broad genus of compositions. Without admitting to the sufficiency of the Examiner's *prima facie* case, applicant respectfully submits that the specification's description of a simple, routine, test for identifying compositions that are driable pediculostatic agents, in conjunction with further guidance as to the compositions most usefully so tested, three identified species, and actual experimental examples, provides sufficient teaching to provide objective enablement across the claimed breadth.

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[12] *In re Marzocchi*. 169 USPQ 367. 369 (CCPA 1971).

The fact that experimentation may be required to select agents that act as driable pediculostatic agents is of no moment:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is "undue," not "experimentation." The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (finding extensive screening of hybridomas not "undue" in the immunologic arts) (internal quotations and citations omitted); *accord, The Johns Hopkins University v. Cellpro Inc*, 47 USPQ2d 1705 (Fed. Cir. 1998).

> Where the specification provides guidance in selecting the operating parameters that would yield the claimed result, it is fair to conclude that the experimentation required to make a particular embodiment is not "undue."

PPG Indus., Inc. v. Guardian Indus. Corp., 37 USPQ2d 1618 (Fed. Cir. 1996).

As described explicitly in applicant's specification, the experimentation required to determine whether a composition is a driable pediculostatic composition can routinely be performed using an eye dropper, a microscope slide, a sharp object, and slight

magnification. Furthermore, applicant provides 8 pages of guidance as to the chemical compositions that are most usefully subject to such test,[13] further identifying three specifies, one of which is demonstrated in experimental examples to have superb efficacy in the claimed methods.

With respect, applicant submits that the specification enables across the entire scope of protection sought, and that the rejection is in error and should be withdrawn.

Rejections under 35 U.S.C. § 112, ¶ 2

The Examiner's rejection of claim 5 under 35 U.S.C. § 112, ¶ 2 has been obviated by amendment.

Rejections under 35 U.S.C. § 102

Rejections under 35 U.S.C. § 102(b) have been obviated by cancellation of claims 29 and 30.

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[13] Specification p. 22, line 13 - p. 31, line 30.

Rejections under 35 U.S.C. § 103

The Examiner rejects claims 1 - 39 under 35 U.S.C. § 103(a) as obvious over Snyder[14] in view of Iannantuno *et al.*[15], Leslie *et al.*[16], and Clore *et al.*[17]

Not one of the cited references teaches, discloses, or suggests a critical step of applicant's claimed methods: ***the drying*** of the driable pediculostatic agent *in situ* (claim 1 step (b)). Such missing element is neither inherent in the cited art nor can be imputed to the ordinarily skilled artisan without impermissible hindsight reconstruction using knowledge of the applicant's disclosure. Accordingly, applicant submits that the rejection fails, and respectfully requests that it be withdrawn.

Conclusion

Rejections and objections under 35 U.S.C. §§ 102, 112, ¶ 2, and 37 C.F.R. § 1.75 have been obviated by amendment. In light of the foregoing discussion, applicant requests reconsideration and withdrawal of rejections under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 103. Applicant invites the Examiner to telephone the undersigned

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[14] U.S. Patent No. 6,063,771.

[15] Iannantuno *et al.*, "Pediculicidal activity of an antidandruff shampoo in a 1% copper-oleate formulation," *Advances in Therapy* 14(3):134 - 139 (May/June 1997).

[16] Belgian Patent No. 868239 (1978).

[17] Clore *et al.*, "A comparative study of seven pediculicides and their packaged nit removal combs," *J. Pediatr. Health Care* 7(2):55 - 60 (1993).

attorney of record if any remaining matter might more expeditiously be handled by telephonic interview.

Respectfully submitted,

2 MARCH 2001

Daniel M. Becker
Reg. No. 38,376
Attorney for Applicants
FISH & NEAVE
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020-1104
Tel.: (650) 617-4000 (California)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Campbell et al.	Art Unit:	1615
Serial No.:	10/692,979	Examiner:	Levy, Neil S.
Filed:	October 24, 2003	Confirmation Number	1729
Title:	METHODS AND COMPOSITIONS FOR TREATING ECTOPARASITE INFESTATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. WILLIAM CAMPBELL UNDER 37 C.F.R §1.132

I, Dr. William Campbell, declare:

1. I am a named inventor in the above-referenced patent application, and the Director of Research and Development at Piedmont Pharmaceuticals, LLC., the assignee of the application. Prior to joining Piedmont Pharmaceuticals, I was a research scientist and senior toxicologist in the Agricultural Division of Ciba (now Syngenta), the manager of new product safety for Ciba Animal Health (now Novartis Animal Health), and the manager of safety and new product development for Blue Ridge Pharmaceuticals. I have designed and supervised testing of compositions described in the present application for treatment of ectoparasite infestations, and so provide this declaration based on my personal knowledge and belief.

2. Head lice are blood sucking insects that lose water by evaporation from the general body surface, spiracles (breathing holes), regurgitation, and excretion of waste. If a head louse is to survive, these losses must be kept to a minimum, and offset by water gained from other sources (such as human blood). Water loss from the insects is normally minimal through the cuticle (the outer layer of the exoskeleton), with loss prevented by the epicuticular lipids of the outer layer of the cuticle, consisting primarily of wax.

3. To determine the activity of isopropyl myristate (IPM) against lice, a study was conducted to expose lice on human subjects to various compositions, including ones consisting of 100% IPM, 50% IPM: 50% cyclodimethicone (D5 siloxane), and 100% D5. In the IPM compositions, the D5 was provided to serve as a spreading agent to facilitate wetting of the hair and spreading of the IPM throughout the hair and scalp. The lice were exposed to the compositions for 10 minutes and their condition observed at 24 hours. At that time point, all of the lice treated with the 100% IPM composition were dead and 91.3% of the lice treated with the 50:50 IPM/D5 composition were dead, while only 78.4% of the lice treated with the 100% D5 composition were dead.

4. To determine a mode of action for IPM against lice, lice were treated for 10 minutes in a Petri dish with the 100% IPM or 50:50 IPM/D5 compositions. As shown in the attached photographs, the dead lice exhibited a shriveled and dried appearance consistent with dehydration. On microscopic evaluation, the loss of the waxy cuticle layer and subsequent loss of body fluids was observed as an opaque "halo" surrounding the body of each louse. Removal of the waxy cuticle allowed unchecked water loss and subsequent dehydration to occur.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: May 24, 2007

Signed at: Greensboro, North Carolina

William R. Campbell

Dr. William Campbell

Top Photo: Lice exposed to 50% IPM solution.

Bottom Photo: Lice exposed to 100% IPM solution.